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BERESKIN AND PARR SCOTIA PLAZA 40 KING STREET WEST-SUITE 4000 BOX 401 TORONTO, ON M5H 3Y2 CANADA				WEHBE, ANNE MARIE SABRINA
		ART UNIT		PAPER NUMBER
		1632		
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/046,542	Applicant(s) JEFFERIES ET AL.
	Examiner Anne Marie S. Wehbe	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 27 April 2004.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-20 is/are pending in the application.
4a) Of the above claim(s) 13 is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 1-12 and 14-20 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 15 May 2002 is/are: a) accepted or b) objected to by the Examiner.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____

DETAILED ACTION

Applicant's response to the restriction/election requirement received on 4/27/04 has been entered. Applicant's election without traverse of the subject matter of Group I, and further the species "gene inducible by tapasin" in claim 10 and the species "tapasin" as the accessory molecule in claim 11, is acknowledged. Claims 1-20 are pending in the instant application. Of these, claim 13 is withdrawn as being directed to subject matter non-elected without traverse in the response received on 4/27/04. Claims 1-12, and 14-20 are currently under examination. An action on the merits follows.

Restriction/Election

Applicant's election of the subject matter of group I is acknowledged. The applicant has not provided any arguments traversing the grounds for restriction and election of species. Therefore, the restriction requirement is still deemed proper and is made FINAL.

It is noted that claims 1, 3-4, 12, and 14-15 have not been amended to reflect the elected subject matter. The applicant is notified however that the elected claims have only been examined to the extent that the read on the elected subject matter, wherein the agent is nucleic acid sequence encoding a TAP molecule.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 4-5, 7, 9, and 14-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,361,770 B1 (3/26/02), hereafter referred to as the '770 patent. . Although the conflicting claims are not identical, they are not patentable distinct from each other for the following reasons. Claims 1-10 of the '770 patent represent a species of the instant broader claims. It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann* , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). The claims of the '770 patent are limited to an *ex vivo* method of augmenting the immune response to a tumor by introducing a nucleic acid encoding TAP-1 into a tumor cell *ex vivo* and introducing the tumor cell into the mammal (claims 1-6), and methods of augmenting the immune response to a tumor by directly introducing a vaccinia virus encoding TAP-1 into a tumor (claims 7-10). Note as well that claims 3 and 9 recite the further administration of a nucleic acid encoding an antigen, and that claim 4 recites wherein the nucleic acid is in a viral vector. Thus, as a species of the instant broader claims, claims 1-10 of the '770 patent render the instant claims obvious.

Claim Rejections - 35 USC §112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, and 14-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) methods of augmenting a CTL response in a mammal to tumor cells expressing low or nondetectable levels of peptide/MHC class I complexes on the cell surface comprising ex-vivo introduction of a nucleic acid encoding TAP-1 into the tumor cells followed by introduction of the tumor cell into the mammal, 2) methods of augmenting a CTL response in a mammal to a tumor cell expressing low or nondetectable levels of peptide/MHC class I on the cell surface comprising introducing a vaccinia virus encoding TAP-1 into the tumor cell, and 3) in-vitro methods of enhancing a CTL response to VSV antigens in a cell expressing low or nondetectable levels of peptide/MHC I on the cell surface comprising, introducing into said cell a nucleic acid comprising a sequence encoding TAP-1 or TAP-2, does not reasonably provide enablement for methods of enhancing any type of immune responses to tumor cells comprising transfecting tumor cells ex vivo or in vivo with any nucleic acid encoding TAP-2, or methods of enhancing any type of immune response to any viral antigen in a cell comprising transfecting the cell in vitro or in vivo with TAP-1 or TAP-1 alone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification discloses the transfection of cells, preferably tumor cells, that have low to undetectable levels of TAP-1 and TAP-2, and low levels of MHC class I on the cell surface, with either TAP-1 or the TAP-2 resulting in increased surface expression of endogenous peptide/MHC class I complexes on the cell surface. The specification further discloses that the target cells transfected with TAP-1 or TAP-2 will express enhanced levels of peptide/MHC leading to an enhanced immune surveillance of the peptides in the host. In addition, the

specification discloses said method wherein the target cell additionally has a deficiency in proteasome components, where TAP-1 or TAP-2 is introduced into the cell as a viral vector, and wherein the endogenous peptide is a viral or tumor antigen.

At the time of filing, the skilled artisan did not consider the transfection of either TAP-1 or TAP-2 alone into cells expressing little to no TAP-1 and TAP-2 as sufficient to enhance or increase presentation of endogenous peptide/MHC class I on the cell surface. Several independent researchers at the time of filing had demonstrated that transfection of TAP-1 or TAP-2 alone into TAP-1/TAP-2 negative cells neither increased the level of MHC class I expression on the cell surface nor resulted in increased peptide specific CTL lysis. Spies et al. transfected 721.174 cells, which have a deletion in both TAP genes, with TAP-1 (PSF-1) and showed that TAP-1 alone was incapable of increasing surface expression of MHC class I (Spies et al., (1991) *Nature*, Vol. 351, page 323, abstract and Figure 1). Whereas Spies et al. looked at presentation of endogenous self-antigens, Momberg et al. demonstrated that T-2 cells, which are also TAP-1/TAP-2 negative, required transfection of both TAP-1 and TAP-2 in order to present endogenous viral antigens derived from Influenza virus in the context of MHC class I for surface expression and CTL recognition and lysis (Momberg et al. (1992) *Nature*, Vol. 360, page 174, Tables 1+2, and page 175, Figure 1). As Povis et al. states, "...the integrity of both transporter polypeptides is required for any significant class I membrane expression or cytosolic peptide presentation. This conclusion is consistent with a model in which the two transporter polypeptides are required to associate in order to form a functional heterodimer" (Povis et al., (1991), *Nature*, Vol. 354, page 531, paragraph 2). Thus, in view of the state of the art at the time of filing, the artisan would not have predicted that MHC class I expression and CTL specific

lysis of target cells could be increased by the transfection of any TAP-1/TAP-2 negative cells line with either TAP-1 or TAP-2 alone.

Regarding the enhancement of anti-viral immune responses, the applicant provides several in vitro working examples of the instant invention regarding the enhancement of viral peptide specific CTL responses with TAP molecules. In vivo examples involving viral peptide presentation are not provided. RMA-S cells, which have mutation in TAP-2, and CMT.64 cells, which the applicant demonstrates are deficient in TAP-1, TAP-2, and the proteasome components LMP-2 and 7, are used in the in vitro working examples. The applicant first demonstrates that untransfected RMA-S cells do not require TAP-2 in order to effectively present VSV derived peptides in the context of MHC class I on the cell surface as measured by VSV specific CTL lysis of VSV infected RMA-S cells. CMT.64 cells, however, which are deficient in both TAP-1 and TAP-2, are unable to present VSV peptide/MHC class I on the cell surface without γ -IFN treatment. The applicant goes on to show that CMT.64 cells transfected with TAP-1 and infected with VSV have increased surface expression of peptide bound MHC class I on the cell surface as measured by FACS analysis, and that CMT.64 cells transfected with either TAP-1 or TAP-2 can be recognized and lysed by VSV specific CTL. However, TAP-2 transfected CMT.64 cells show approximately half the amount of specific lysis than TAP-1 transfected cells, and neither TAP-1 nor TAP-2 transfected cells are lysed as efficiently as untransfected CMT.64 cells loaded with exogenous VSV peptide. In addition, the applicant demonstrates that CMT.64 transfected with TAP-1 and infected with Influenza are not lysed by Influenza specific CTL suggesting that TAP-1 is not sufficient to allow processing and presentation of endogenous Influenza peptides in CMT.64 cells (specification , page 36, lines 9-

15). Finally, The applicant's working example using HSV infected CMT.64 cells shows that HSV peptides are processed and presented independent of TAP-1 and TAP-2 as untransfected CMT.64 cells infected with HSV are lysed with equal efficiency as TAP-1 transfected CMT.64 (specification, page 36, lines 35-38). Viewed as a whole, the applicant's in vitro working examples demonstrate that of the viral antigens tested, only VSV peptides are capable of being processed, presented, and expressed on the cell surface of CMT.64 cells in the context of MHC class I following transfection of the cells with TAP-1 or TAP-2 and recognized by viral specific CTL. Therefore, based on the stated of the art of enhancing immune responses by introducing TAP molecules, the breadth of the claims, and the working examples which show that transfection of the CMT.64 cells with either TAP-1 or TAP-2 did not enhance Influenza peptide presentation and recognition by CTL, and HSV peptides are presented independent of TAP expression, the skilled artisan would not have been able to predict in the absence of undue experimentation whether the MHC class I presentation of any viral peptides other than VSV peptides could be enhanced by the transfection of TAP-1 or TAP-2 alone in cells which lack expression of both TAP-1 and TAP-2.

At the time of filing, the generation of immune responses against tumor antigens was further complicated by mutations in the tumor cells and nature of tumor antigens as self antigens. Restifo et al. teaches that tumors evade immune response by a variety of mechanisms besides down-regulation of putative antigen processing molecules such as TAP and MHC-encoded proteasome components, including loss of antigenic epitopes by either lack of expression or mutations, loss of functional β_2 m expression , and loss particular MHC class I alleles (Restifo et al (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). The loss or

mutation of any of these molecules would prevent the expression of tumor specific peptide/MHC class I complex on the cell surface regardless of the presence or absence of TAP-1 or TAP-2. Another important aspect of the immune response to a tumor is the activity of natural killer cells. NK cells recognize and kill cells with down regulated MHC class I on the cell surface. Several groups have demonstrated that NK lysis of tumor cells is the predominant immune response to certain types of tumors. Franksson et al. showed that the murine lymphoma cell line RMA-S which has a deletion in TAP-2 generates an effective anti-tumor NK response resulting in decreased tumor growth (Franksson et al. (1993) J. Exp. Med., Vol. 177, page 202, Table 1 and Figure 1). In contrast, RMA-S cells transfected with TAP-2, which demonstrated enhanced presentation of peptide/MHC class I and sensitivity to CTL, were particularly tumorigenic *in vivo* due to the loss of NK cell lytic activity (Franksson et al., page202, Table 1 and Figure 1). The specification does not address how cells of the instant method could augment an NK mediated immune response, or provide guidance as to the characteristics of tumors that require a CD8+ CTL response rather than an NK response for immune eradication. Thus, the skilled artisan would not have had a reasonable expectation of generating or augmenting any immune response to any and all tumors deficient in TAP-1 and TAP-2 by introducing either TAP-1 or TAP-2.

Furthermore, the art at the time of filing did not consider gene therapy of cancer, particularly human cancer, using transduced or transfected tumor cells as predictable. Orkin et al. identifies several strategies for increasing anti-tumor immune responses including, “ the transfer of genes for ... immunomodulatory products to cancer cells”, either *ex vivo* or *in vivo*, “ in an attempt to stimulate immune recognition of not only the gene modified cancer cells, but

also cancer cells that have not received the gene..", and concludes that, " [a]lthough several of these strategies show promise in mouse models, none has demonstrated efficacy in humans" (Orkin et al. (1995) "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy", page 6, paragraph 5).

In support of the enhancement of presentation of endogenous tumor antigens and enhancement of anti-tumor immune responses, the applicant has provided several working examples which demonstrate that the transfection of tumor cells with low or nondetectable levels of peptide/MHC class I complexes on the cell surface either *ex vivo* with TAP-1 nucleic acid or *in vivo* with vaccinia virus encoding TAP-1 enhances surface expression of peptide/MHC class I complexes and enhances tumor specific CTL responses. However, the working examples provided also clearly demonstrate that transfection with TAP-2 alone is not effective, see examples 21 and 22, particularly page 74. Thus, in view of the high degree of unpredictability in art at the time of filing for generating anti-tumor immune responses by transfecting MHC class I low/negative cells with TAP-1 or TAP-2 alone, and applicant's data which demonstrates that while TAP-1 transfection can increase anti-tumor CTL responses TAP-2 transfection cannot, the skilled artisan would not have been able to predict without undue experimentation whether transfection of TAP-2 alone into any tumor type would be capable of enhancing any type of anti-tumor immune response.

In addition, the specification's working examples are limited to the direct administration of recombinant vaccinia virus encoding TAP-1 at or near the site of a tumor. The specification does not provide working examples demonstrating the use of other types of plasmid or viral vectors *in vivo* or other routes of delivery of TAP-1 to tumor cells other than delivery to the site

of the tumor in the mammal. The specification also fails to provide sufficient guidance for using vectors other than vaccinia virus to deliver TAP-1 to tumor cells or any other type of cell *in vivo*. In particular, the specification does not provide sufficient guidance concerning dosages and routes of *in vivo* delivery for any and all vectors which encode TAP-1, such as retrovirus, adenovirus, or plasmid vectors, wherein an enhanced anti-tumor immune response is observed. The art of time of filing considered the targeted *in vivo* delivery of recombinant vectors, and the expression of therapeutic levels of the encoded transgenes in the target cells as unpredictable. Verma et al. teaches that, " ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2). Miller et al. supplements Verma et al. by teaching that successful gene therapy requires the delivery of the gene to the appropriate cell both efficiently and accurately and states that currently, " ..improvements to the accuracy of a vector often compromise its efficiency, and vice versa" (Miller et al. (1995) FASEB, Vol. 9, page 190, columns 1-2 bridging paragraph). The specification does not teach strategies to target vector to tumor cells *in vivo* other than by direct, localized injection of the vector into the tumor itself. Thus, based on the unpredictable effects of gene delivery using both viral and non-viral vectors as taught by the art at the time of filing, and the lack of guidance provided by the specification for the use of any and all vectors and routes of *in vivo* vector delivery other than the direct administration of vaccinia virus encoding TAP-1 to the tumor site, it would have required undue experimentation for the skilled artisan to practice the instant invention as claimed.

Regarding other aspects of the invention, it is noted that the specification fails to provide any description or enabling disclosure for a “gene inducible by tapasin”. While the applicant’s claims encompass potentially large number of nucleotide sequences, the instant specification fails to teach any gene which is inducible by tapasin or the nucleic acid sequence corresponding to any such gene. The specification further fails to provide any description of the particular physical, chemical, and biological features of a gene which is inducible by tapasin such that nucleic acid sequences corresponding to such genes could be identified. As such, the skilled artisan would not have been able to identify or use any “gene inducible by tapasin” without undue experimentation. See also the rejection of claim 10 for lack of written description below.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim recites a method of enhancing an immune response to an antigen comprising administering a nucleic acid encoding a TAP molecule and a gene inducible by tapasin. The specification fails to provide adequate written description for any gene which is inducible by tapasin. While the applicant’s claims encompass potentially large number of nucleotide sequences, the instant specification fails to teach any gene which is inducible by tapasin or the nucleic acid sequence of any such gene. The specification further fails to provide any description of the particular physical, chemical, and biological features of a gene which is inducible by tapasin such that nucleic acid sequences corresponding to such genes could be identified. The Revised Interim Guidelines state “ when there is substantial variation with the

genus, one must describe a sufficient variety of species to reflect the variation within the genusIn an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). In the absence of any description of any gene which is inducible by tapasin, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids or the primers or probes needed for detection of such genes in any organism. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for genes inducible by tapasin. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 and 14-20 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is a step or limitation which relates the administration of a nucleotide encoding a TAP molecule that can augment the level of a TAP molecule in a target cell to the enhancement of an immune response to an antigen.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7-8, 16, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Spies et al. (1992) Nature, Vol. 355, 644-646. The applicant claims methods of enhancing an immune response to an antigen comprising administering a nucleic acid encoding a TAP molecule to a cell or animal. The claims methods further comprise wherein the target cell is a virally infected cell or a tumor cell, wherein the TAP molecule is TAP-1, wherein the TAP

nucleic acid is in a plasmid vector, or wherein a nucleic acid encoding a viral antigen is further administered to the cell or animal. Please note that the claims as written read broadly on cells *in vitro* or *in vivo*, and methods of enhancing immune responses *in vitro* or *in vivo*.

Spies et al. teaches that enhancement of CTL response against a tumor cell following the co-administration of a vaccinia virus encoding a viral antigen and plasmid vector encoding TAP-1 to the cells *in vitro* (Spies et al., pages 644-645, especially Figure 1). Thus, by teaching all the limitations of the claims, Spies et al. anticipates the instant invention as claimed.

Claims 1-4, 6,-8, 16, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Powis et al. (1991) *Nature*, Vol. 354, 528-531. The applicant claims methods of enhancing an immune response to an antigen comprising administering a nucleic acid encoding a TAP molecule to a cell or animal. The claims methods further comprise wherein the target cell is a virally infected cell or a tumor cell, wherein the TAP molecule is TAP-2, wherein the TAP nucleic acid is in a plasmid vector, or wherein a nucleic acid encoding a viral antigen is further administered to the cell or animal. Please note that the claims as written read broadly on cells *in vitro* or *in vivo*, and methods of enhancing immune responses *in vitro* or *in vivo*.

Powis et al. teaches the enhancement of CTL response against a tumor cell following the co-administration of influenza virus, which encodes influenza viral antigens, and a plasmid vector encoding TAP-2 to the cells *in vitro* (Powis et al., page 531, Figure 4). Thus, by teaching all the limitations of the claims, Powis et al. anticipates the instant invention as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read "Anne M. Wehbé".